AWARD NUMBER: W81XWH-16-2-0038

TITLE: The Genomic Epigenomic, and Quality-of-Life Charteristics of Long-Term Survivors of Ovarian Cancer

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REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE:	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE

The Genomic Epigenomic, and Quality-of-Life Charteristics of Long-Term Survivors of Ovarian Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER

W81XWH-16-2-0038

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Ovarian cancer (OC) remains a major health problem in the United Sates (US). In 2012, there will be an estimated 22,280 cases of epithelial OC (EOC) resulting in 15,500 deaths. While the median survival of OC patients has improved over the last two decades, the vast majority of patients suffer relapse and develop chemo-resistant disease. The overall survival of patients suffering from OC has not changed appreciably over the last three decades. Despite these dismal statistics, there is a minority of OC patients who are long-term (LT) survivors (>10 years). This includes a subset of advanced stage (~15%) and a higher proportion of early-stage disease (75%). Unfortunately, there is little genomic or biologic characterization of these tumors, or patient reported outcomes that characterize LT survivors. The clinical importance of identifying subsets of patients who may or may not benefit from therapy, and understanding the biology of their tumors, is significant both from a patient survival and quality of life (QOL) standpoint. The characterization of LT survivors of advanced stage OC will potentially identify molecular and clinical pathways that can be targeted to help women who have shorter survivals. Further, careful characterization of these patients, including their initial and longitudinal health-related QOL reports, their response to treatments, and their tumors will provide significant measures of prognostic factors. Accurate identification of women with high-grade, early stage OC who will recur will allow for tailoring therapy to only those who will benefit. Thus, the systematic molecular and patient-reported outcomes evaluation of LT survivors of OC (both early and advanced stage) will yield data, which can significantly impact the management of OC patients.

15. SUBJECT TERMS					
Ovarian cancer, long-term survival, consortium development, genomics, epigenomics, quality of life, psychosocial					
16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT U Unclassified	**b. ABSTRACT** U Unclassified	**c. THIS PAGE** U Unclassified	UU Unclassified	8	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Introduction

Background: Ovarian cancer (OC) remains a major health problem in the United Sates (US). In 2012, there will be an estimated 22,280 cases of epithelial OC (EOC) resulting in 15,500 deaths. While the median survival of OC patients has improved over the last two decades, the vast majority of patients suffer relapse and develop chemo-resistant disease. The overall survival of patients suffering from OC has not changed appreciably over the last three decades. Despite these dismal statistics, there is a minority of OC patients who are long-term (LT) survivors (>10 years). This includes a subset of advanced stage (~15%) and a higher proportion of early-stage disease (75%). Unfortunately, there is little genomic or biologic characterization of these tumors, or patient reported outcomes that characterize LT survivors. The clinical importance of identifying subsets of patients who may or may not benefit from therapy, and understanding the biology of their tumors, is significant both from a patient survival and quality of life (QOL) standpoint. The characterization of LT survivors of advanced stage OC will potentially identify molecular and clinical pathways that can be targeted to help women who have shorter survivals. Further, careful characterization of these patients, including their initial and longitudinal health-related QOL reports, their response to treatments, and their tumors will provide significant measures of prognostic factors. Accurate identification of women with high-grade, early stage OC who will recur will allow for tailoring therapy to only those who will benefit. Thus, the systematic molecular and patient-reported outcomes evaluation of LT survivors of OC (both early and advanced stage) will yield data, which can significantly impact the management of OC patients.

Overall Aim: To characterize the genomic, biologic, and quality of life for LT survivors of EOC. We hypothesize that LT survivors of OC have distinct features that distinguish them from short-term (ST) survivors.

KEYWORDS: Ovarian cancer, long-term survival, survivorship, consortium development, genomics, epigenomics, quality of life

Research Accomplishments

Major Task 1: HRPO approval of Consortium IRB protocols
We have obtained IRB and HRPO approval for three different human research protocols:

1) Title "The coordinating center for the consortium of long-term survivors of ovarian cancer" – this protocol was approved by MGH IRB, Michael Birrer PI, and describes the process by which deidentified biological and quality of life data are shared across the consortium.
2) Title "The Genomic, Epigenomic and Psychosocial Characteristics of Long-Term Survivors of Ovarian Cancer – Recruitment" – This protocol was approved at MGH, Michael Birrer PI and describes the process by which patients are recruited to the study and their QOL data and tumor samples are collected
3) Genomic, Epigenomic and Psychosocial Characteristics of Long-Term Survivors of Ovarian Cancer- approved at UCI, PI Lari Wenzel, this study describes the process by which patients recruited to the study at MGH connect with Lari Wenzel to perform follow up phone interviews on their quality of life

The project is currently being transferred to UAB where a new IRB approved protocol is being established.

Major Task 2: Analysis of 132 tumor samples from GOG 182 and GOG 172 clinical trials
The tumor samples have been identified and collected by GOG and then distributed to MGH. The patient population included in these samples consists of women who were diagnosed with high grade serous ovarian cancer at FIGO stage 3 or 4 and survived 1+ years. One third of these patients survived 8+ years and were defined as LTS, the remaining 2/3 presented a survival distribution that reflected the survival distribution in real world, i.e. with most patients surviving between 2-4 years; these were defined as STS.

Sequential sample slides of these tumors were distributed to all research sites of the consortium responsible for tumor molecular analysis: INOVA (proteomics), MD Anderson (miRNA-seq), IU (methylaetion), CHUV (IHC for immune infiltrations), MGH (RNAseq). Genomics/proteomics analysis by each participating site was performed using their specific platforms and the data were shared with Victoria Wang for integration. IHC analysis for immune infiltration has been delayed due to ongoing analysis of 340 samples collected through a different award, and included in this research project, from patients diagnosed with serous high grade ovarian cancer at FIGO stage 1 (see next task). Figures 1 and 2 show the results obtained from three platforms: miRNAseq, RNAseq, proteomics.

The global genomics data for each platform (before integration) were presented at the Consortium annual meeting at MGH on 09/22/2017. Data integration, as well as functional analysis for the different signatures that were identified to be differently distributed between LTS and STS is ongoing.

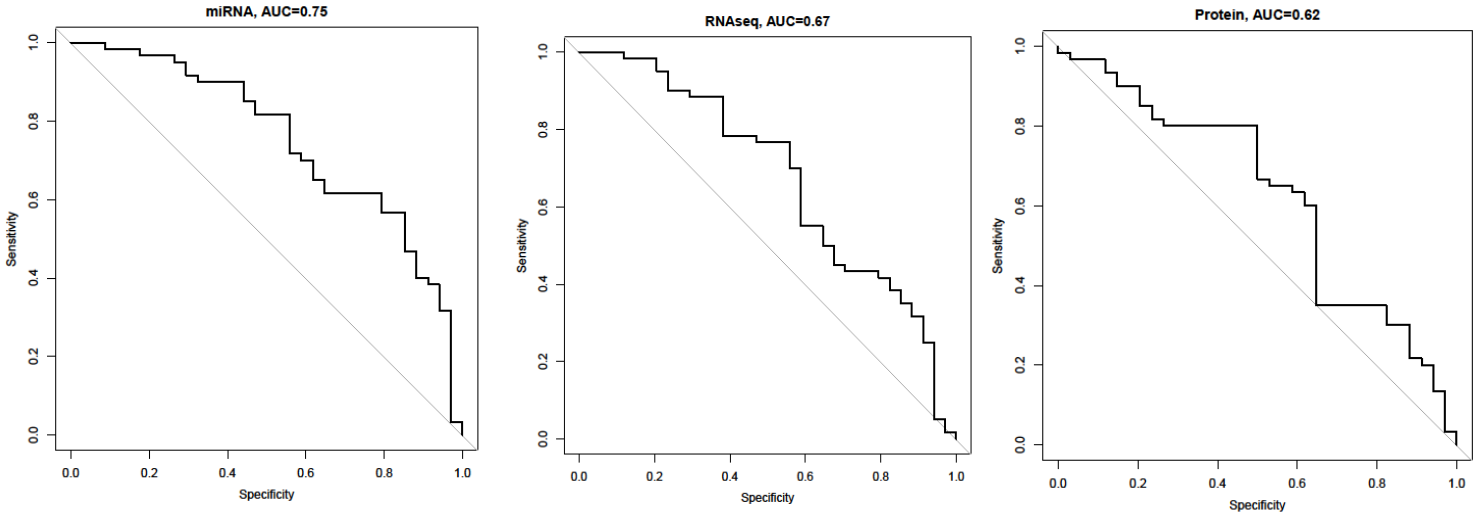

Figure 1: Molecular signatures predicting long-term survival.
For each molecular data type (miRNAseq left, RNAseq middle, proteomics right), we have identified a preliminary signature consisting of a small number of molecular features to predict LTS status. A 5-fold cross-validation scheme is used to select the best model and assess signature performance. For each fold, models are built on 4/5 of the data and tested on the remaining 1/5. Areas under the ROC curve (AUC) are computed on the test data to evaluate prediction accuracy. Our median cross-validated AUCs for our best models so far are 0.67 for RNAseq, 0.75 for miRNA-seq and 0.62 for proteomics, and are expected to improve with larger sample size and integration of different data types; these will be obtained from analysis of GOG218 scheduled in year 2.

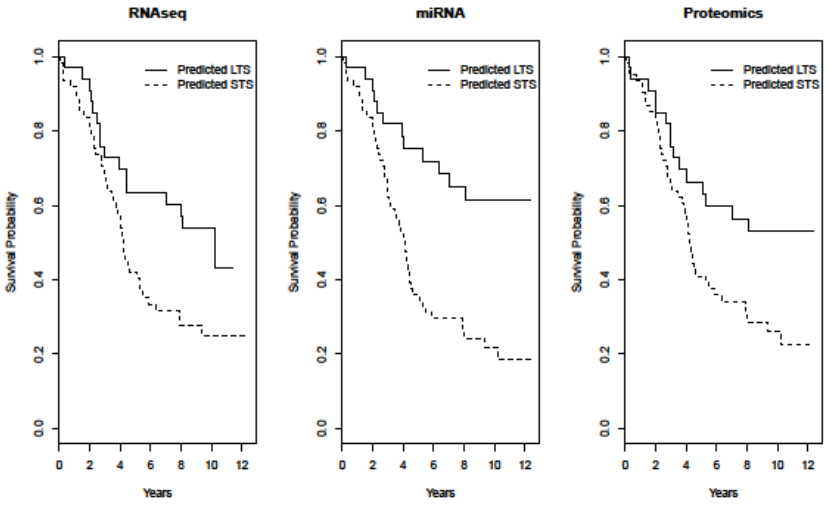

Figure 2: Kaplan Meier analysis of the signature obtained from each molecular analysis shown in Figure 1.
Each signature identified to predict LTS in Figure 1 correlates with longer survival in our cohort.

Milestone #3: Identification of a signature for early stage OC recurrence and comparison with LTS preliminary signature.

We have accomplished the analysis of 340 tumor samples from patients diagnosed with ovarian cancer at early stages. The scope of this analysis is to identify a signature for recurrence of early stage tumors (Figures 3 and 4). The genomics and IHC analysis of these samples can then be integrated with the data obtained from advanced tumors to identify the real differences existing between tumor diagnosed at early stage versus those diagnosed at advanced stage.

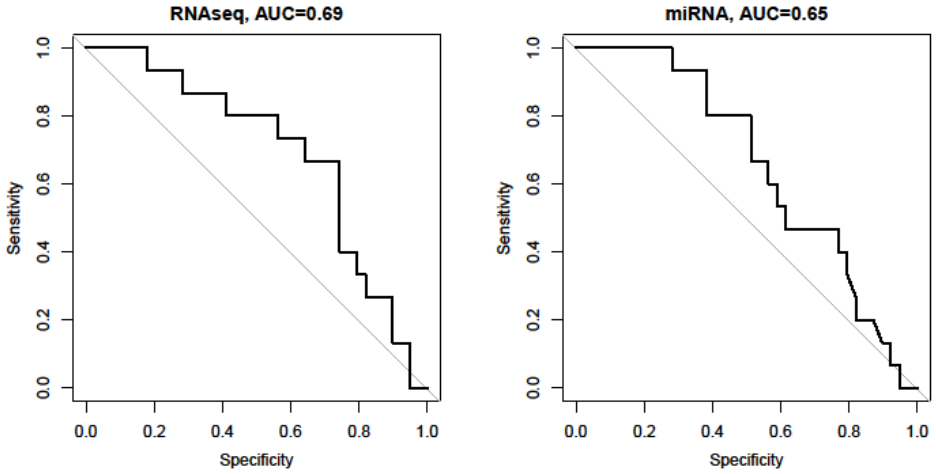

Figure 3: Signatures for recurrence in early stage tumors obtained through RNAseq and miRNAseq

130 of 340 samples have been set aside as a validation set and the same cross-validation scheme described above has been used for model building using the remaining 210 samples to predict recurrence. We have built an mRNA expression signature consisting of about 50 features for the endometrioid tumors with median cross-validated AUC of 0.69. The median cross-validated AUC for our best miRNA model is 0.65.

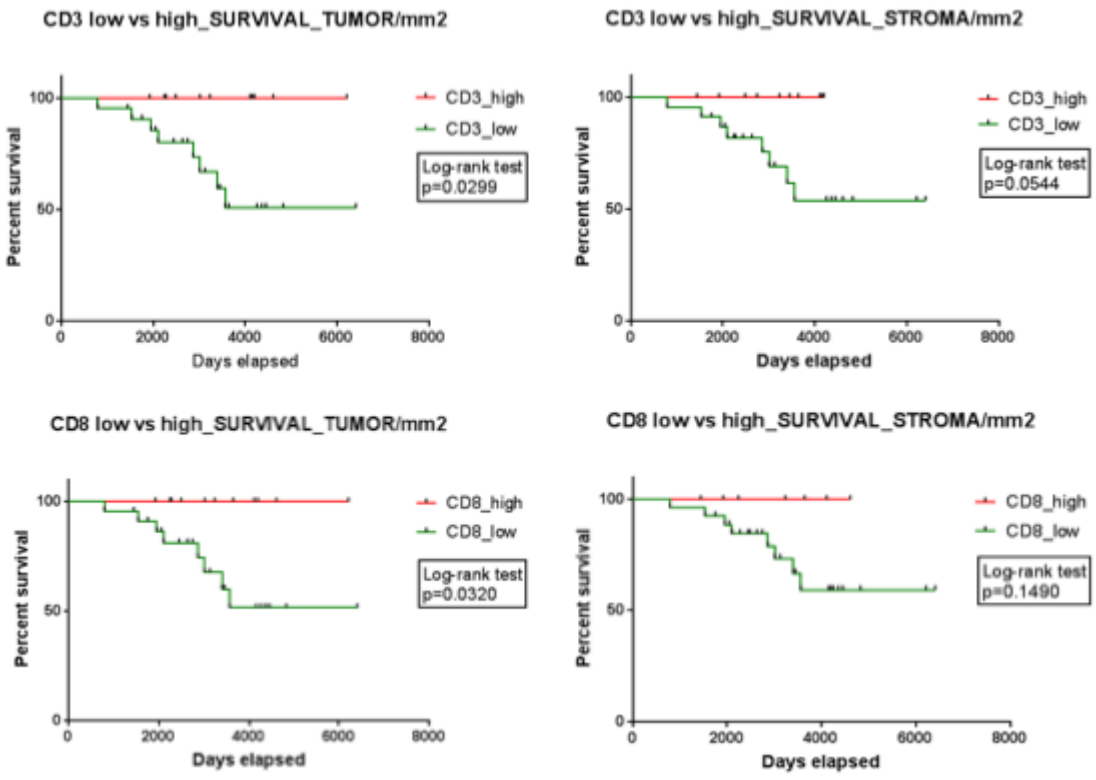

Figure 4: IHC analysis of immune cells in early stage tumors.

CD3 and CD8 immune markers predict for non-recurrence in early stage tumors

Major Task 5: Retrieval of other, non-GOG samples

We have collected 20 tumor samples from LTS that were treated at MGH, however, only for 6 of these patients was possible to have them participate in a QOL survey. Due to the PI's transfer to UAB we decided not to pursue collection of tumor samples from B&W, but instead to collect samples from UAB.

We are in process of establishing a collaboration with the Texas tumor registry to exploit the diversified population of that registry for tumor collection and performance of QOL analysis

We are in process of signing an MTA agreement with LeCharite, Berlin Germany, for the collection of 50 LTS tumors and corresponding 150 STS tumors. The samples have been sequenced by DNAseq.

We are in process of signing a collaboration agreement with ICORG to exploit their organized hospital network and collect tumor samples as well as QOL data from Irish patients

We have enrolled LTS from the general USA population and collected 54 QOL surveys followed by phone interviews and collected tumor samples from 15 of these patients.

A biorepository with associated database for LTS has been established. Our goal is to collect overall 300 tumors (100 LTS + 200 STS) and for the 100 LTS survivors gather complete QOL data

Other Achievements: N/A

Plans for the next reporting period: N/A

Results disseminated to communities of interest: This work is being developed with the active participation of 9 patients advocates affiliated with ovarian cancer foundations that act as Partners in this project (Table 1). Through their activity the study was divulgated to the general population as described above.

Table 1

Advocate Advisory Board Members	
Name	**Partner Organization**
Mary Jackson Scroggins, Chair	In My Sister's Care
April Donahue	National Ovarian Cancer Coalition (NOCC)
Anne Marie DeCarlo	Ovarian Cancer Research Fund Alliance (OCRFA)
Martha ("Meg") Gaines	Center for Patient Partnerships (CPP)
Venus Ginés	Día de la Mujer Latina (DML)
Henrietta Ho-Asjoe	Charles B. Wang Community Health Center
Deborah Miller	GOG Patient Advocate Committee (PAC)
Chrystine Tedeschi	SHARE
Marsha Wilson	Foundation for Women's Cancer (FWC)

Actual or anticipated problems or delays and actions or plans to resolve them: There may be delays in accomplishing all the milestones described for year 2 of this award due to the transfer of the award, and thus the Consortium Coordinating Center to the University of Alabama Birmingham.

IMPACT

Impact on the development of the principal discipline(s) of the project: A global systemic analysis of advanced stage ovarian cancers that includes both quality of life and tumor biology allows performing multivariate analysis that includes: stress/inflammatory/immune factors, overall wellbeing of the patient, reported toxicities during treatment, and survival. This is an un-precedent analysis that can be done by our consortium as we leverage the accurate QOL database collected by the GOG Foundation. In addition, this work allows studying cases of ovarian cancer as chronic disease. Indeed, many long-term survivors included in our study maintain active cancer throughout their survivorship or continue develop recurrences and/or other tumors. These are both very important areas in the future of cancer research.

Impact on other disciplines: Nothing to report

Impact on technology transfer: Nothing to Report

Impact on society beyond science and technology: This is the first systemic study being developed with such a strong engagement of the patients advocates. AAB members participated in this project not only by helping in drafting the QOL survey, but also by helping divulgating the study and educating other patients about the importance of research. Their participation in this study will benefit exclusively the future generations and this message is being divulgated throughout the community. Our goal in Phase II will be to create a community of patients that are directly engaged in the development of this project. Our continuous communication with these patients allows development of the tools we use for the QOL studies as well as possibilities in the future to collect more tissues from these very rare patients.